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Determinants of Utility Based on the EuroQol Five-Dimensional Questionnaire in Patients with Chronic Heart Failure and Their Change Over Time: Results from the Swedish Heart Failure Registry

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ABSTRACT

Background: There is limited information on drivers of utilities in patients with chronic heart failure (CHF). **Objectives:** To analyze determinants of utility in CHF and drivers of change over 1 year in a large sample from clinical practice. **Methods:** We included 5334 patients from the Swedish Heart Failure Registry with EuroQol five-dimensional questionnaire information available following inpatient or outpatient care during 2008 to 2010; 3495 had 1-year follow-up data. Utilities based on Swedish and UK value sets were derived. We applied ordinary least squares (OLS) and two-part models for utility at inclusion and OLS regression for change over 1 year, all with robust standard errors. We assessed the predictive accuracy of both models using cross-validation. **Results:** Patients' mean age was 73 years, 65% were men, 19% had a left ventricular ejection fraction of 50% or more, 23% had 40% to 49%, 27% had 30% to 39%, and 31% had less than 30%. For both models and value sets, utility at inclusion was affected by sex, age, New York Heart Association class, ejection fraction, hemoglobin, blood pressure, lung disease, diabetes, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, nitrates, antiplatelets, and diuretics. The OLS model performed slightly better than did the two-part model on a population level and for capturing utility ranges. Change in utility over 1 year was influenced by age, sex, and (measured at inclusion) disease duration, New York Heart Association class, blood pressure, ischemic heart disease, lung disease, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and antiplatelets. **Conclusions:** Utilities in CHF and their change over time are influenced by diverse demographic and clinical factors. Our findings can be used to target clinical interventions and for economic evaluations of new therapies.

Keywords: chronic heart failure, EQ-5D, value set, utilities.

Introduction

Chronic heart failure (CHF) is associated with high morbidity and mortality, as well as large reductions in health-related quality of life (HRQOL) [1,2]. Although the incidence and the mortality of CHF have generally decreased over time, disease burden remains high due to a significant need for specialized and hospital care [2,3]. As new treatment strategies are emerging for CHF, for both patients with preserved and with reduced left ventricular ejection fraction (LVEF) [4], it is important to be able to evaluate these therapies in terms of their clinical benefit and cost-effectiveness.

In economic evaluations, effectiveness outcomes are generally measured using quality-adjusted life-years, an aggregate measure for length and quality of life. Quality-adjusted life-years are calculated by weighing survival with a utility score between 0 and 1, where 1 represents perfect health and 0 death (or a health state equivalent to death in the eyes of the respondent). Utilities can be derived from responses to generic HRQOL instruments through algorithms based on different valuation methods (e.g., time trade-off or standard gamble) [5]. Values for different health states derived from, for example, the generic EuroQol five-dimensional questionnaire (EQ-5D) instrument are commonly referred to as value sets; an important distinction lies in whether

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the valuations are elicited from individuals with experience of the health state (experience-based values) or from individuals from the general population to whom the health states are described (hypothetical values) [6].

Understanding the determinants of utility in a patient group allows adjusting for differences in populations when combining diverse data sources in economic models. Moreover, it provides information on factors that may be influenced through patient management. The strong link between HRQOL in CHF and morbidity and mortality makes it particularly important to understand which factors have an impact on utility as an aggregate measure of HRQOL (e.g., [7–9]). Independent determinants of HRQOL in CHF include age, sex, New York Heart Association (NYHA) class, LVEF, clinical parameters, comorbidities, medications, and previous hospitalizations [10–14]. To our knowledge, however, the only published utility function available in CHF to date is based on the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study [12], in which HRQOL was modeled on the basis of the EQ-5D. Thus, there is a need for analyses based on clinical practice, taking into account a wide range of demographic and clinical parameters. The main objective of our study was to analyze the impact of different determinants on utilities in CHF, including a range of demographic and clinical parameters, and to analyze the impact of different factors on change in utility over 1 year.

Methods

Study Population

The Swedish Heart Failure Registry (SHFR) was created in 2003 with the goal of improving the management of patients with CHF [15]. Patients are included at discharge from hospital (within 1 month) or following an outpatient visit, and registered variables include demographic characteristics and disease information, comorbidities, diagnostic procedures, hemodynamics, laboratory data, medications, CHF symptoms, and HRQOL. After 1 year, all patients receive a questionnaire on HRQOL, functional capacity, and current medications [15]. In 2010, 84% of Swedish hospitals and 6% of Swedish primary care units were reporting into the SHFR. By the end of 2010, 36911 patients had been included in the registry, corresponding to an estimated mean patient coverage of 61% among participating hospitals [16].

In the SHFR, the HRQOL has been measured with the EQ-5D as part of the 1-year follow-up since 2005, and as part of baseline registrations since 2008. The EQ-5D covers five dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a visual analogue scale. In the established three-level version, each attribute can be described as causing no problems, some problems, or major problems [17].

We obtained data for all patients included in the SHFR until December 31, 2010, who had responded to the EQ-5D at either inclusion and/or 1-year follow-up. Comparisons between those with complete EQ-5D information and the overall registry were made using the 2010 annual report from the SHFR [16]. To describe the impact of CHF on HRQOL relative to the general population, the EQ-5D responses were compared with published Swedish population values [18].

Statistical Methods

Variable Definitions

Answers to the EQ-5D were translated into utilities by using a recently published value set for Sweden, which uses experience-based preferences [6]. The main analysis thus reflects preferences in the same local context as the SHFR. Because general population preferences are used in several jurisdictions, secondary results are also presented on the basis of the commonly used UK value set [19].

Age was transformed into a categorical variable using 10-year age bands (<60 years, 60–69 years, 70–79 years, ≥80 years), which are most often used in the literature. *Inpatient setting* was defined as during or subsequent to an inpatient stay, including those referred to a heart failure clinic/care team, and *outpatient setting* as involving outpatient specialists or primary care physicians. The glomerular filtration rate was estimated on the basis of the Modification of Diet in Renal Disease equation [20].

Covariate Selection Process

Variables were selected for testing on the basis of expected clinical relevance and findings from previous studies and included age group, sex, point of care (inpatient/outpatient), duration of CHF (<6 months or ≥6 months), NYHA class reported by the clinician at inclusion, comorbidities (hypertension, atrial fibrillation, diabetes, lung disease, ischemic heart disease, valvular heart disease, dilated cardiomyopathy), LVEF (≥50%, 40%–49%, 30%–39%, <30%), systolic blood pressure (SBP), heart rate, estimated glomerular filtration rate, hemoglobin, performed procedures (cardiac revascularization, device therapy, cardiac valvular surgery), and medications at inclusion (angiotensin-converting enzyme [ACE] inhibitors/angiotensin receptor blockers [ARBs], beta-blockers, diuretics, aldosterone antagonists, digitalis, statins, long-acting nitrates, antiplatelets). Potential explanatory variables with strong correlations (Pearson's $r \geq 0.6$) were excluded from further regression analyses to avoid multicollinearity. Each candidate predictor was examined individually using univariate regression models with robust standard errors. Variables statistically significant at the $P < 0.1$ level in univariate analyses were included in subsequent multivariate regressions; based on clinical rationale, age and sex were always retained. For the change analysis, all significant drivers of baseline utility were included in the initial multivariate model. The final models were based on covariates significant at the $P < 0.05$ level.

Model Selection and Specification: Baseline Utility

Because of their boundedness and a common ceiling effect (often with a "spike" at the upper bound for the EQ-5D), utilities do not follow the distributional assumptions required to make an inference about the significance of coefficients from ordinary least squares (OLS) regression. Given our research objective, that is, to determine drivers of mean utility in a population that can also be used in economic evaluations, and the relative ease of interpretation of outputs, we used OLS with robust standard errors as the main approach [21,22]. In view of the high proportion of values at the ceiling (0.97/1 using the Swedish/UK value set), however, we also tested two-part models as an alternative method frequently discussed in the literature [21,23]. The first part predicts the probability of an individual obtaining the EQ-5D ceiling value by using logistic regression, and the second part models the EQ-5D index value for those whose scores are below the ceiling using OLS regression. For both regression steps, robust standard errors were used. All covariates found to be significant in either the logistic or the OLS model were included in the final two-part model.

In both approaches, we tested to include the following interactions in the final models, based on clinical hypotheses and earlier studies on determinants of HRQOL in CHF [12,24–26]: age/sex and NYHA class, age/sex and number of comorbidities, and age/sex/number of comorbidities and LVEF, respectively. Finally, we performed comprehensive diagnostic testing of model fit and specification, including scatter plots of model residuals versus fitted values, goodness of fit (R^2 for OLS, Hosmer-Lemeshow

for logistic regression), linktest for model specification, and receiver operating characteristic for logistic regression.

Model Validation

To assess the predictive accuracy of the OLS and two-part modeling approaches, we performed empirical cross-validation by randomly splitting the data set into a training (90%) and validation (10%) set. For the two-part model, the expected utility for a patient was calculated as described previously [23]. We compared the predicted versus observed means on an aggregate level (using paired Student *t* tests), the range of predictions, and the errors between the actual and predicted individual utilities (mean squared error, mean absolute error; with bootstrapped 95% confidence intervals) [27,28]. For the Swedish value set, this was also performed by age category.

For covariates for which more than 5% of the observations were missing, that is, NYHA class and LVEF, we performed multiple imputations as part of a sensitivity analysis. We used chained imputation with ordered logistic regression (m = 20). Because the largest spread of values can be expected for the UK value set, we compared the results of the two regression models applied to this value set by deriving utilities for hypothetical patients from the mild and severe end of the spectrum.

Model Selection and Specification: Change in Utility

For determinants of change in utility over 1 year, we applied OLS regression to model the absolute change score, applying robust standard errors to account for the high kurtosis in the outcome distribution.

All analyses were performed in Stata/SE 10.0 (StataCorp, College Station, TX, USA).

Results

General

Baseline characteristics are presented in Table 1. At inclusion in the registry, 5334 patients had completed the EQ-5D, which corresponds to 14% of the patients in the SHFR at the time of data extraction (38% of the patients included during 2008–2010). Compared with the entire SHFR population, patients who had completed the EQ-5D were on average slightly younger, more often male, had more complete information on NYHA class and slightly better renal function, and received ACE inhibitors/ARBs more often and diuretics less often (Table 1).

At 1-year follow-up, 3495 (66%) patients in our sample had completed the EQ-5D. Among these, mean age was 71.8 years and utility 0.846 at inclusion; that is, loss to follow-up occurred to a higher degree among older patients and among those with lower baseline utility. Mean utility was 0.840 ± 0.126 after 1 year compared with 0.846 ± 0.127 for the same patients at inclusion.

HRQOL in Patients with CHF Compared with the General Population

Compared with a similar age group (70–79 years) in the Swedish general population [18], HRQOL in patients with CHF at inclusion was negatively affected in the domains of mobility, self-care, and anxiety/depression, while slightly fewer patients with CHF reported moderate or severe problems with usual activities (Fig. 1).

Determinants of Utility at Inclusion

Results of the OLS and two-part regressions for utilities based on the Swedish value set are presented in Table 2. For both methods, utility was affected in the same direction by sex, age, NYHA class, LVEF, hemoglobin, SBP, lung disease, diabetes, ACE inhibitors/ARBs, nitrates, antiplatelets, and diuretics. In the OLS model, beta-blockers were also significant, whereas in the two-part model, hypertension and previous revascularization were significant instead. Moreover, we found a significant interaction between age categories and NYHA class. The interaction implies that patients younger than 60 years are more severely affected by increasing NYHA status than are those older than 60 years.

Results of the OLS and two-part regressions for utilities based on the UK value set are presented in Table 3. The same coefficients were found to be significant, with the same direction of change, as for the Swedish value set, except that beta-blockers instead of previous revascularizations were significant in the two-part model. As shown in Table 1, utilities were markedly higher when using the Swedish value set instead of the UK value set, with a smaller range and an upper bound at 0.97 instead of 1. Consequently, the magnitude of model coefficients differs for the two value sets. For applications in a Bayesian framework, the covariance matrix for the identified covariates based on the UK value set is available as a supplementary table (see Appendix Table S1 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2015.02.003).

Comparison of Predictive Accuracy of Models at Inclusion

Results of the cross-validation for the OLS and two-part models are summarized in Table 4. For the Swedish value set, the mean predicted utility was numerically closer to the observed mean when using the OLS model, although mean absolute error and mean squared error were slightly better for the two-part model. Overall, the OLS model generated a somewhat broader range of predictions, although it still did not capture the whole spectrum of observed values. For the UK value set, the two-part model provided slightly more precise predictions than did the OLS model in terms of mean predicted utility (although not statistically significant), mean absolute error, and mean squared error. As for the Swedish value set, the predicted range was better using the OLS model.

When analyzing predictions by age groups for the Swedish value set, these were least precise in those younger than 60 years (data not shown). In this age group, the OLS model produced better predictions in terms of mean and range, with similar error to the two-part model. For those aged 60 to 69 years, the two-part model was slightly better in terms of mean prediction and error, whereas the OLS model more satisfactorily captured especially the lower range of predictions. In those aged 70 to 79 years, the two-part model was slightly preferable to the OLS model in terms of range and error, but with less precise prediction of the mean. Finally, in those older than 80 years, the two-part model performed better regarding mean prediction and range, with a similar mean error as the OLS model. The differences in mean predictions, however, were statistically significant only for the two-part model in the youngest age group.

We found the predicted utilities based on the imputed data to be very similar to the complete case regression (difference 0.01–0.02).

Determinants of Change over 1 Year

Results of the multivariate regression for change in utilities based on the Swedish value set are presented in Table 5 (results based on the UK value set are available in Appendix Table S2 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2015.02.003). Absolute change over 1 year for those with follow-up information was affected by age, sex, and the following variables at inclusion: NYHA class, disease duration, SBP, ischemic heart disease, lung disease, ACE inhibitors/ARBs, and antiplatelets.

Table 1 – Baseline characteristics for patients who completed the EQ-5D at inclusion and 1-y follow-up, compared with all patients in the SHFR (2010).

Variable	All patients in SHFR	Patients with the EQ-5D at inclusion	Patients with the EQ-5D at follow-up
Demographic characteristics			
Number of patients	36,911	5,334	3,495
Age at inclusion (y)	74.8	72.9 ± 11.4	71.8 ± 11.0
Sex: female (%)	39	35	34
Point of care (%)			
Inpatient care and referrals to outpatient heart failure clinics	94	79	82
Outpatients in primary care and specialist care	6	21	18
Disease characteristics at discharge/after visit			
Duration of heart failure (%)			
<6 mo	48	49	55
≥6 mo	52	51	45
Unknown/missing	NA	1	1
NYHA class (%)			
I	6	10	11
II	32	44	49
III	27	33	31
IV	4	3	2
Unknown	30	9	8
LVEF (%)			
≥50	19	17	16
40–49	19	20	21
30–39	24	24	26
<30	25	28	28
Unknown/missing	13	12	10
Clinical findings at discharge/after visit			
Weight (kg)	NA	79 (18)	79 (18)
Systolic blood pressure (mm Hg)	128	128 (21)	128 (21)
Heart rate (beats/min)	75	73 (15)	72 (15)
Hemoglobin (g/L)	132	133 (17)	135 (16)
Creatinine (μmol/L)	112	105 (54)	100 (46)
eGFR (mL/min)	60	64 (26)	66 (26)
Comorbidities (past or present) (%)			
Ischemic heart disease	47	44	42
Hypertension	46	49	47
Atrial fibrillation	47	46	45
Valvular heart disease	19	18	17
Dilated cardiomyopathy	11	14	15
Diabetes	24	23	20
Lung disease	18	18	16
Performed procedures (ever) (%)			
Cardiac revascularization	24	26	26
Cardiac valvular surgery	5	5	6
Device therapy	13	12	11
Medications at discharge/after visit (%)			
ACE inhibitors/ARBs	80	88	91
Beta-blockers	83	87	88
Diuretics	87	76	75
Aldosterone antagonist	21	25	25
Digitalis	18	17	16
Statins	42	50	52
Anticoagulants	35	41	43
Antiplatelets	53	49	47
EQ-5D index value (Swedish value set)			
Mean ± SD	NA	0.828 ± 0.135	0.846 ± 0.126
Median	NA	0.868	0.880
Range (min, max)	NA	(0.340, 0.969)	(0.340, 0.969)
EQ-5D index value (UK value set)			
Mean ± SD	NA	0.696 ± 0.302	0.732 ± 0.275

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Table 1 – *continued*

Variable	All patients in SHFR	Patients with the EQ-5D at inclusion	Patients with the EQ-5D at follow-up
Median	NA	0.743	0.796
Range (min, max)	NA	(−0.594, 1)	(−0.594, 1)
% of responses at ceiling (either value set)	NA	25	27

Notes. Numbers present mean values ± SD or proportion, as appropriate. Information on all SHFR patients based on 2010 annual report. Figures for point of care are not entirely comparable across data sets because of coding differences. The NYHA was rated by a clinician. Medications refer to 2010 only.

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; EQ-5D, EuroQol five-dimensional questionnaire; LVEF, left ventricular ejection fraction; NA, not available; NYHA, New York Heart Association; SHFR, Swedish Heart Failure Registry.

Discussion

This appears to be the first study to analyze determinants of utility in CHF in a large sample of patients from clinical practice. We identified several important drivers of utility at inclusion, including age, sex, NYHA class, LVEF, hemoglobin, SBP, lung disease, diabetes, ACE inhibitors/ARBs, beta-blockers, nitrates, antiplatelets, and diuretics. Change in utility over 1 year among survivors was influenced by age, sex, and (measured at inclusion) disease duration, NYHA class, SBP, ischemic heart disease, lung disease, ACE inhibitors/ARBs, and antiplatelets.

The interaction in the model between age and NYHA class at inclusion could be explained by a higher general expected utility in the youngest age group, and a potential for higher incremental losses in HRQOL and utility for these patients when they develop symptoms. Descriptive analyses (results not presented) showed that anxiety/depression is more negatively affected in the youngest age group, compared with an otherwise larger proportion of younger respondents stating no problems in the other dimensions.

Different methods have been proposed to address the distributional properties of utility data, including Tobit, censored least absolute deviations, two-part, latent class, and beta models [21–23,29,30]. Some of the methods tested previously in the literature, such as Tobit or censored least absolute deviations, have been criticized for their censoring assumptions [21]. To date, no model has been found to address all concerns and issues related to utility data. Therefore, the choice of the model will depend on the data at hand and the research objectives. For instance, the

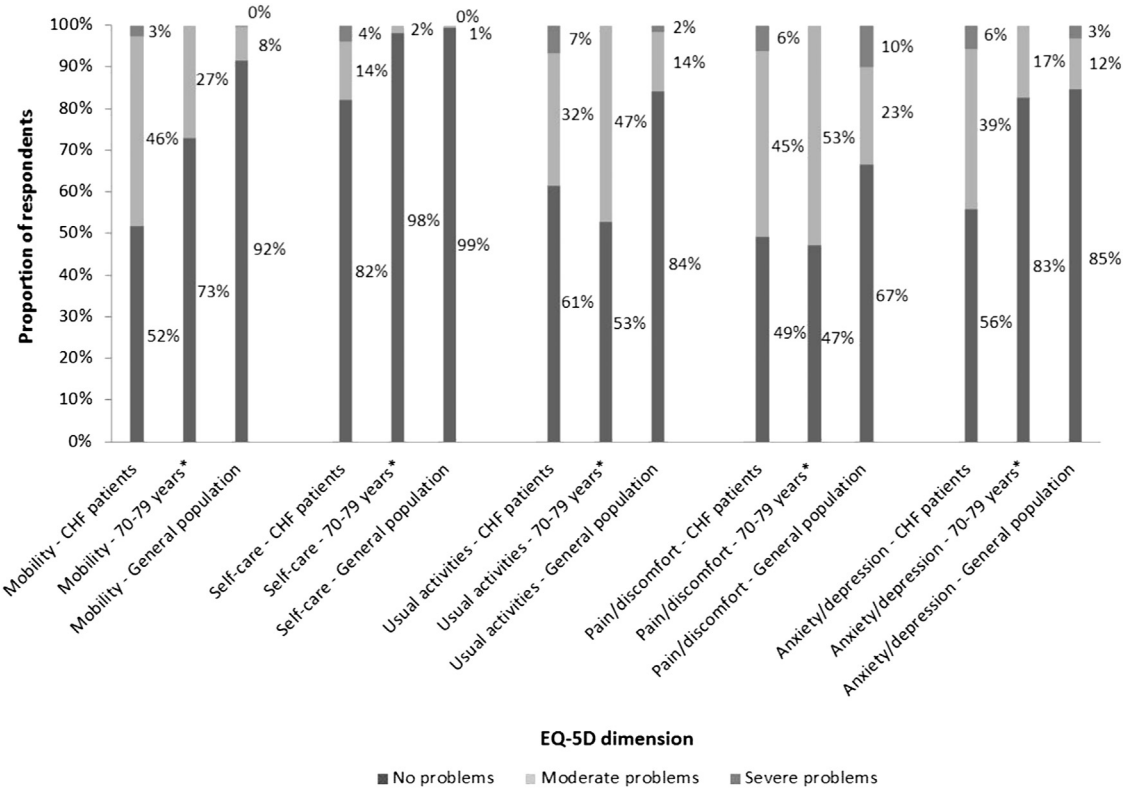

Fig 1 – Distribution of responses by severity level in the EQ-5D dimensions, for patients with CHF at inclusion, the general Swedish population (16–84 years), and a comparable age group (70–79 years). *Note.* **Only moderate or severe problems reported for 70- to 79-year-olds. EQ-5D, EuroQol five-dimensional questionnaire; CHF, chronic heart failure.**

Table 2 – Final model specifications for determinants of utility at inclusion using the Swedish value set, for OLS and two-part models.

Variable	OLS (n = 4147)				Two-part: Logistic (n = 3982)				Two-part: OLS (n = 2924)			
	Coefficient	95% CI		P	Odds ratio	95% CI		P	Coefficient	95% CI		P
Demographic characteristics												
Sex: female	−0.037	−0.045	−0.029	0.000	0.597	0.498	0.716	0.000	−0.027	−0.037	−0.018	0.000
Age0: <60 y		Reference group				Reference group				Reference group		
Age1: 60–69 y	−0.005	−0.026	0.016	0.660	0.848	0.468	1.536	0.586	−0.006	−0.050	0.039	0.796
Age2: 70–79 y	−0.023	−0.045	−0.001	0.041	0.553	0.316	0.966	0.037	−0.023	−0.065	0.018	0.267
Age3: ≥80 y	−0.037	−0.063	−0.011	0.006	0.395	0.212	0.736	0.003	−0.031	−0.074	0.011	0.149
Disease characteristics												
NYHA I		Reference group				Reference group				Reference group		
NYHA II	−0.068	−0.089	−0.047	0.000	0.331	0.199	0.551	0.000	−0.071	−0.109	−0.032	0.000
NYHA III	−0.150	−0.178	−0.123	0.000	0.072	0.037	0.140	0.000	−0.110	−0.151	−0.069	0.000
NYHA IV	−0.265	−0.370	−0.161	0.000	0.051	0.006	0.412	0.005	−0.179	−0.285	−0.072	0.001
Age1 × NYHA II	0.029	0.002	0.056	0.035	1.342	0.690	2.611	0.387	0.041	−0.009	0.090	0.109
Age1 × NYHA III	0.042	0.007	0.076	0.017	1.990	0.874	4.534	0.101	0.029	−0.023	0.082	0.272
Age1 × NYHA IV	0.051	−0.069	0.171	0.403	0.000	0.000	0.000	0.000	0.015	−0.109	0.139	0.813
Age2 × NYHA II	0.042	0.015	0.069	0.003	1.426	0.763	2.667	0.266	0.061	0.015	0.107	0.009
Age2 × NYHA III	0.051	0.017	0.085	0.003	3.022	1.391	6.567	0.005	0.037	−0.012	0.086	0.136
Age2 × NYHA IV	0.054	−0.062	0.170	0.362	2.050	0.180	23.399	0.564	0.001	−0.117	0.120	0.982
Age3 × NYHA II	0.041	0.010	0.072	0.009	1.921	0.960	3.841	0.065	0.052	0.005	0.100	0.031
Age3 × NYHA III	0.068	0.032	0.105	0.000	2.674	1.148	6.227	0.023	0.058	0.008	0.107	0.022
Age3 × NYHA IV	0.086	−0.025	0.196	0.130	0.745	0.041	13.636	0.843	0.038	−0.076	0.152	0.513
LVEF ≥50%		Reference group				Reference group				Reference group		
LVEF 40%–49%	0.016	0.004	0.028	0.008	1.439	1.105	1.873	0.007	0.008	−0.005	0.022	0.204
LVEF 30%–39%	0.028	0.017	0.040	0.000	1.788	1.379	2.319	0.000	0.019	0.006	0.031	0.003
LVEF <30%	0.031	0.019	0.042	0.000	2.270	1.746	2.950	0.000	0.014	0.001	0.027	0.032
Clinical parameters												
Hemoglobin (g/L)	0.000	0.000	0.001	0.000	1.007	1.002	1.012	0.005	0.000	0.000	0.001	0.006
Systolic blood pressure (mm Hg)	0.001	0.000	0.001	0.000	1.008	1.004	1.012	0.000	0.000	0.000	0.001	0.001
Comorbidities												
Hypertension	NS				0.814	0.691	0.959	0.014	0.006	−0.003	0.015	0.189
Lung disease	−0.019	−0.028	−0.009	0.000	0.762	0.614	0.946	0.014	−0.016	−0.026	−0.006	0.003
Diabetes	−0.022	−0.031	−0.013	0.000	0.896	0.737	1.089	0.270	−0.025	−0.035	−0.015	0.000
Performed procedures (ever)												
Revascularization	NS				0.944	0.783	1.139	0.550	0.014	0.004	0.024	0.006
Medications												
ACE inhibitors/ARBs	0.035	0.021	0.049	0.000	1.473	1.081	2.008	0.014	0.032	0.018	0.046	0.000
Beta-blockers	0.014	0.003	0.025	0.013	NS				NS			
Nitrates	−0.019	−0.031	−0.008	0.001	0.711	0.540	0.937	0.015	−0.012	−0.024	0.001	0.074
Antiplatelets	−0.012	−0.019	−0.004	0.002	0.884	0.751	1.042	0.142	−0.013	−0.022	−0.004	0.004
Diuretics	−0.012	−0.021	−0.004	0.005	0.803	0.671	0.960	0.016	−0.008	−0.019	0.002	0.131
Constant	0.759	0.712	0.806	0.000					0.740	0.680	0.800	0.000
Fit statistics												
R^2		0.235								0.170		
Pseudo R^2						0.128						

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CI, confidence interval; LVEF, left ventricular ejection fraction; NS, not significant; NYHA, New York Heart Association; OLS, ordinary least squares.

Table 3 – Final model specifications for determinants of utility at inclusion using UK value set, for OLS and two-part models.

Variable	OLS (n = 4147)				Two-part: logistic (n = 4000)				Two-part: OLS (n = 2940)			
	Coefficient	95% CI		P	Odds ratio	95% CI		P	Coefficient	95% CI		P
Demographic characteristics												
Sex: female	−0.077	−0.096	−0.058	0.000	0.602	0.503	0.720	0.000	−0.057	−0.078	−0.036	0.000
Age0: <60 y		Reference group				Reference group				Reference group		
Age1: 60–69 y	−0.030	−0.079	0.018	0.222	0.803	0.442	1.458	0.471	−0.063	−0.155	0.028	0.176
Age2: 70–79 y	−0.067	−0.116	−0.018	0.008	0.534	0.306	0.932	0.027	−0.078	−0.159	0.003	0.060
Age3: ≥80 y	−0.101	−0.159	−0.044	0.001	0.368	0.197	0.686	0.002	−0.092	−0.175	−0.009	0.029
Disease characteristics												
NYHA I		Reference group				Reference group				Reference group		
NYHA II	−0.150	−0.193	−0.107	0.000	0.312	0.187	0.520	0.000	−0.162	−0.234	−0.090	0.000
NYHA III	−0.325	−0.388	−0.262	0.000	0.069	0.036	0.134	0.000	−0.232	−0.314	−0.149	0.000
NYHA IV	−0.631	−0.875	−0.388	0.000	0.050	0.006	0.400	0.005	−0.492	−0.778	−0.206	0.001
Age1 × NYHA II	0.088	0.027	0.148	0.004	1.420	0.728	2.772	0.304	0.157	0.055	0.259	0.003
Age1 × NYHA III	0.119	0.039	0.199	0.003	2.100	0.919	4.798	0.078	0.125	0.011	0.238	0.031
Age1 × NYHA IV	0.159	−0.117	0.436	0.259	0.000	0.000	0.000	0.000	0.161	−0.159	0.481	0.324
Age2 × NYHA II	0.104	0.044	0.163	0.001	1.508	0.807	2.818	0.198	0.168	0.077	0.260	0.000
Age2 × NYHA III	0.146	0.068	0.223	0.000	3.111	1.432	6.760	0.004	0.130	0.027	0.232	0.013
Age2 × NYHA IV	0.175	−0.103	0.453	0.217	2.038	0.179	23.242	0.566	0.106	−0.210	0.422	0.510
Age3 × NYHA II	0.126	0.059	0.194	0.000	2.108	1.054	4.215	0.035	0.172	0.077	0.266	0.000
Age3 × NYHA III	0.192	0.110	0.274	0.000	2.876	1.234	6.701	0.014	0.177	0.074	0.280	0.001
Age3 × NYHA IV	0.247	−0.019	0.513	0.068	0.802	0.044	14.605	0.881	0.203	−0.103	0.510	0.194
LVEF ≥50%		Reference group				Reference group				Reference group		
LVEF 40%–49%	0.030	0.003	0.057	0.031	1.452	1.116	1.891	0.006	0.011	−0.019	0.042	0.463
LVEF 30%–39%	0.064	0.038	0.089	0.000	1.771	1.364	2.299	0.000	0.041	0.012	0.069	0.006
LVEF <30%	0.069	0.043	0.096	0.000	2.250	1.729	2.928	0.000	0.031	0.001	0.062	0.045
Clinical parameters												
Hemoglobin (g/L)	0.001	0.000	0.002	0.002	1.007	1.002	1.012	0.006	0.001	0.000	0.001	0.076
Systolic blood pressure (mm Hg)	0.001	0.001	0.001	0.000	1.008	1.005	1.012	0.000	0.001	0.000	0.001	0.008
Comorbidities												
Hypertension	NS				0.803	0.681	0.946	0.009	0.001	−0.020	0.021	0.945
Lung disease	−0.032	−0.055	−0.010	0.005	0.779	0.627	0.967	0.024	−0.024	−0.049	0.000	0.054
Diabetes	−0.040	−0.062	−0.019	0.000	0.897	0.739	1.090	0.276	−0.041	−0.065	−0.018	0.001
Medications												
ACE inhibitors/ARBs	0.075	0.043	0.107	0.000	1.446	1.061	1.971	0.019	0.067	0.034	0.101	0.000
Beta-blockers	0.037	0.011	0.062	0.005	1.219	0.958	1.551	0.107	0.037	0.007	0.066	0.015
Nitrates	−0.042	−0.069	−0.014	0.003	0.691	0.526	0.908	0.008	−0.021	−0.051	0.009	0.163
Antiplatelets	−0.027	−0.043	−0.010	0.002	0.872	0.747	1.019	0.085	−0.024	−0.043	−0.004	0.016
Diuretics	−0.028	−0.047	−0.009	0.004	0.803	0.672	0.960	0.016	−0.017	−0.041	0.006	0.142
Constant	0.565	0.458	0.672	0.000					0.522	0.390	0.653	0.000
Fit statistics												
R^2		0.203								0.136		
Pseudo R^2						0.128						

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CI, confidence interval; LVEF, left ventricular ejection fraction; NS, not significant; NYHA, New York Heart Association; OLS, ordinary least squares.

Table 4 – Predictive accuracy of OLS and two-part models, for Swedish and UK value sets.

Parameter (valuation set)	OLS				Two-part model			
Sweden	**Mean ± SD**		**Min**	**Max**	**Mean ± SD**		**Min**	**Max**
EQ-5D index	0.835 ± 0.134		0.398	0.969	0.840 ± 0.131		0.398	0.969
Predicted utility	0.837 ± 0.065		0.600	0.977	0.848 ± 0.067		0.625	0.978
	Mean	**SE**	**95% CI (bs)**		**Mean**	**SE**		
MAE	0.091	0.004	0.084	0.099	0.088	0.004	0.082	0.097
MSE	0.014	0.001	0.012	0.016	0.013	0.001	0.011	0.016
UK	**Mean ± SD**		**Min**	**Max**	**Mean ± SD**		**Min**	**Max**
EQ-5D index	0.708 ± 0.307		−0.429	1.000	0.720 ± 0.297		−0.429	1.000
Predicted utility	0.715 ± 0.136		0.158	0.985	0.721 ± 0.127		0.220	0.960
	Mean	**SE**	**95% CI (bs)**		**Mean**	**SE**		
MAE	0.205	0.009	0.188	0.225	0.201	0.009	0.185	0.221
MSE	0.075	0.007	0.063	0.091	0.072	0.007	0.061	0.088

bs, bootstrapped (bias-corrected); CI, confidence interval; MAE, mean absolute error; MSE, mean square error; OLS, ordinary least squares; SE, standard error.

problems with significance and confidence intervals arising when using OLS may to some extent be remedied by using robust standard errors or nonparametric bootstrapping [21], necessitating correct model specification to ensure that the mean is correctly modeled [22]. We found that the performance for the OLS and two-part models varied across different age groups and between value sets. Generally, there was a trend of slightly higher precision for the two-part model on an individual level and for the OLS model on a population level. The OLS model consistently captured the range of observed utilities to a better degree. Therefore, in light of our overall objectives, we believe that the OLS model is a viable primary option for modeling utilities for use in economic evaluations (where population means are of interest) in this data set, owing to its relative accuracy on a population level and its ease of implementation.

Our findings regarding determinants of utility confirm and expand on previous research in this field. For 1628 patients with CHF and recent acute myocardial infarction enrolled in a clinical

Table 5 – Final model specifications for determinants of absolute change in utility from inclusion to 1-y follow-up, using the Swedish value set (N = 2995).

Variable	Coefficient	95% CI		P
Demographic characteristics				
Sex: female	0.000	−0.010	0.011	0.933
Age0: <60 y		Reference group		
Age1: 60–69 y	0.005	−0.012	0.021	0.568
Age2: 70–79 y	0.004	−0.012	0.020	0.593
Age3: ≥80 y	−0.015	−0.033	0.002	0.077
Health status at inclusion				
NYHA I		Reference group		
NYHA II	0.015	0.003	0.027	0.013
NYHA III	0.017	0.003	0.031	0.018
NYHA IV	0.091	0.049	0.134	0.000
Disease duration <6 mo	0.015	0.006	0.025	0.001
Clinical parameters at inclusion				
Systolic blood pressure (mm Hg)	0.000	−0.001	0.000	0.000
Comorbidities at baseline				
Ischemic heart disease	−0.012	−0.022	−0.001	0.026
Lung disease	−0.014	−0.027	−0.001	0.034
Medications at baseline				
ACE inhibitors/ARBs	−0.025	−0.041	−0.008	0.005
Antiplatelets	0.014	0.004	0.025	0.005
Constant	0.056	0.018	0.093	0.003
Fit statistics				
R^2	0.030			

Note. Example for deriving the change in utility: if a patient had a utility of 0.8 at inclusion and all other variables are at the reference level, the change in utility to year 1 would be 0.056; i.e., the utility at 1 y would be 0.8 + 0.056 = 0.856.
ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; CI, confidence interval; NYHA, New York Heart Association.

trial, Gohler et al. [12] developed two separate models for utilities derived from the EQ-5D based on either the NYHA class or the number of cardiovascular rehospitalizations during 18 months of follow-up. Given the multinational nature of the trial, EQ-5D scores were weighted on the basis of relevant preferences for the United States, the United Kingdom, and Latin America; results showed that utilities were highest in the United States. Despite differences in the populations and methodology, we obtained similar results regarding age, sex, NYHA class, and comorbidities (specifically diabetes and lung disease). In addition to a broader patient sample and set of variables in our study, we identified a significant impact of LVEF and different common medications on utility.

The finding that the utility for patients with reduced LVEF was higher than for those with normal LVEF when controlling for other factors is an important addition to previous studies that have evaluated HRQOL in reduced versus preserved LVEF. For example, in a controlled clinical trial setting in the United States, HRQOL measured with the Minnesota Living With Heart Failure Questionnaire was not found to be different between the two patient groups [31], whereas a large cross-sectional retrospective study in outpatient care found preserved LVEF to be independently associated with worse scores on both the Minnesota Living With Heart Failure Questionnaire and the EQ-5D visual analogue scale [11]. Differences in results across studies may be due to variations in the underlying patient samples, study settings, measurement of HRQOL and utility, as well as analytical techniques. This is an area that warrants further research.

Using our OLS model based on the UK value set (to allow comparisons with previous research), the utilities for, for example, male patients with CHF aged 70 to 79 years (with all other variables at the reference level) were found to be 0.50 for NYHA class I, 0.45 for class II, 0.32 for class III, and 0.04 for class IV. In the same patient group, the utility for CHF with preserved ejection fraction (LVEF $\geq$50%) would be 0.50 versus 0.56 to 0.57 for CHF with reduced ejection fraction (LVEF $<$ 40%). Although the evidence around minimum clinically important differences for the EQ-5D is heterogeneous [32], analyses based on instrument-defined health transitions indicate a mean minimally important difference of 0.08 for the EQ-5D for the UK value set and 0.04 for the US value set (which produces a more narrow range of utilities) [33]. This is in line with earlier results [34], and indicates that our model based on a generic HRQOL instrument is capable of capturing clinically important differences between patient groups similar to what has been observed in other studies [12,35].

There are several limitations to our study. First, our sample presents a selected subgroup of patients who completed the EQ-5D at inclusion in the SHFR. These patients differ from the overall SHFR population in that they were slightly younger, more often male, less often in NYHA class IV, and received somewhat different medications. These differences may be due to a larger proportion of patients in our sample stemming from an outpatient setting. Of note, patients captured by the SHFR may not be fully representative of the general CHF population in Sweden because the reporting from primary care is limited [16]. Moreover, compared with a large population-based sample of patients with heart failure in Sweden from 2010 [3], which also included acute disease, patients in the SHFR were slightly younger (75 vs. 77 years), more often men (61% vs. 49%), and less frequently had ischemic heart disease (47% vs. 51%), hypertension (46% vs. 71%), and diabetes (24% vs. 27%), but more often atrial fibrillation (47% vs. 45%). Therefore, our sample is likely not representative of patients in the oldest age groups, all women (which may be related to age), those in NYHA IV, or those managed only in primary care. This could imply an overestimation of utilities in the overall CHF population due to representation in terms of age, sex, and functional class, and potentially an underestimation due to a predominant inclusion from hospitals. The possible impact of differences in comorbidities, however, is difficult to estimate. Although we have adjusted for the known confounders in our analyses, the results inherently do not capture unobserved confounders.

Second, our analyses of drivers of utility evolution over time are limited by the lack of comprehensive information in the SHFR on changes in clinical parameters and events following inclusion in the registry. In addition, there was a considerable loss to follow-up (34%), which partly is due to a high (19%) 1-year mortality [16] and the progressive nature of CHF.

Finally, the utilities are based on a generic HRQOL instrument, which inherently is not as responsive to clinical changes as disease-specific instruments [36,37]. Despite this and a marked ceiling effect, our analyses indicate that it was possible to capture clinically relevant differences in utilities derived from the EQ-5D at inclusion, for example, in terms of NYHA class or LVEF. Moreover, the usefulness of generic HRQOL instruments in CHF has been suggested by a large study investigating drivers of HRQOL in outpatients with CHF [11]; determinants were found to be similar when analyzing scores from the EQ-5D visual analogue scale and the Minnesota Living With Heart Failure Questionnaire as separate outcomes variables.

Notwithstanding these limitations, our analysis has several important strengths. It is based on the largest and most comprehensive sample of patients with CHF to date, covering 5334 patients treated in inpatient and outpatient care. Because of its size and the amount of variables available, it also provides new information on several important subgroups, for example, age, sex, and patients with preserved or reduced LVEF. The focus on a large number of patients with CHF allows for robust estimations regarding variables that are of importance in this population.

From a methodological point of view, we performed comprehensive statistical testing, for example, checking for interaction terms and nonlinearity, and compared different modeling approaches commonly discussed in the literature using within-sample validation. In this context, further research including out-of-sample validation could be of value. Moreover, we present models for estimating utilities in CHF based on two different value sets, which represent both different geographies and valuation methods. Value sets differ between countries because of not only methodological variances but potentially also cultural differences [38]. There is considerable debate and a heterogeneous body of evidence regarding whether experience-based or hypothetical values are to be preferred (e.g., [6,39]). Generally, experience-based values may include adaptation and tend to be higher than hypothetical values, especially for severe health states [6]. Thus, our study provides a comparison and choice between two different approaches and sources, which can be tailored to the decision context.

Conclusions

In this large study of patients with CHF in clinical practice, we have identified a range of demographic and clinical factors that influence utility, both at inclusion and over time. The findings can be used to target clinical interventions and in economic evaluations of new therapies for patients with CHF. Overall, we found that the OLS model addressed our research objective adequately and we provide results for both the Swedish and UK value sets.

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Supplemental Materials

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